

**This Page Is Inserted by IFW Operations
and is not a part of the Official Record**

BEST AVAILABLE IMAGES

**Defective images within this document are accurate representations of
the original documents submitted by the applicant.**

Defects in the images may include (but are not limited to):

- **BLACK BORDERS**
- **TEXT CUT OFF AT TOP, BOTTOM OR SIDES**
- **FADED TEXT**
- **ILLEGIBLE TEXT**
- **SKEWED/SLANTED IMAGES**
- **COLORED PHOTOS**
- **BLACK OR VERY BLACK AND WHITE DARK PHOTOS**
- **GRAY SCALE DOCUMENTS**

IMAGES ARE BEST AVAILABLE COPY.

**As rescanning documents *will not* correct images,
please do not report the images to the
Image Problem Mailbox.**

THIS PAGE BLANK (USPTO)

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification⁵ :

G01N 33/543, B03C 1/035, 1/28

A2

(11) International Publication Number:

WO 91/11716

(43) International Publication Date:

8 August 1991 (08.08.91)

(21) International Application Number: PCT/US91/00664

(22) International Filing Date: 31 January 1991 (31.01.91)

(30) Priority data:

443,077

31 January 1990 (31.01.90)

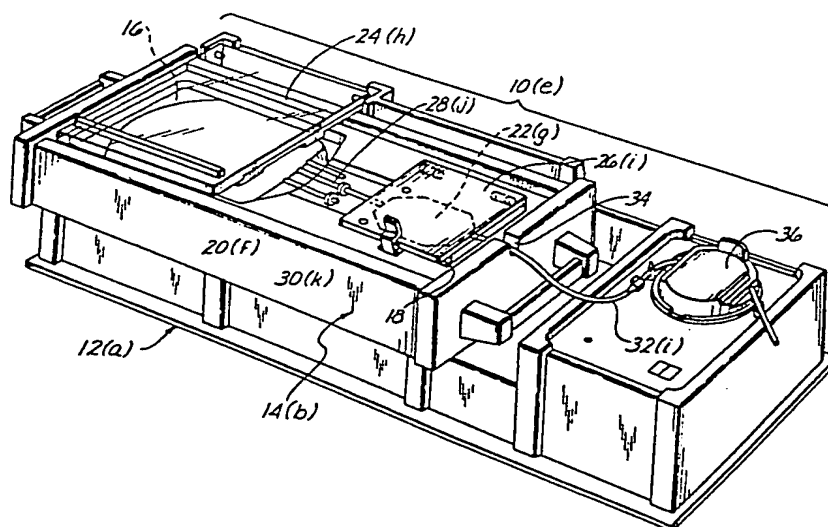
US

(71) Applicant: BAXTER INTERNATIONAL INC. [US/US];
One Baxter Parkway, Deerfield, IL 60015 (US).(72) Inventors: HARDWICK, R., Alan ; 22842 Cedarspring, El
Toro, CA 92630 (US). JOHNSON, Kenneth, M. ; 1905
Burr Oak Lane, Lindenhurst, IL 60046 (US). LYNN,
Daniel, R. ; 37162 N. Lakeshore Drive, Lake Villa, IL
60046 (US).(74) Agents: SCHIFFER, Michael, G. et al.; 2132 Michelson
Drive, Irvine, CA 92715-1304 (US).(81) Designated States: AT (European patent), BE (European
patent), CA, CH (European patent), DE (European pa-
tent), DK (European patent), ES (European patent), FR
(European patent), GB (European patent), GR (Euro-
pean patent), IT (European patent), JP, LU (European
patent), NL (European patent), SE (European patent).

Published

*Without international search report and to be republished
upon receipt of that report.*

(54) Title: FLEXIBLE BAG ASSEMBLY FOR MAGNETIC SEPARATOR



(57) Abstract

A flexible container arrangement useful for performing the magnetic separation of paramagnetic particles from a heterogeneous biological mixture. The flexible container arrangement of the invention includes two or more flexible containers (20, 22) having inlet and outlet ports. A flexible conduit (32) is connected between an outlet port of a first container and an inlet port of a second container. Another flexible conduit (32) is connected between an outlet port of the second container to allow for the discharge of fluid. The second flexible container (20, 22) is designed to provide for a reduction in fluid velocity at a rate of from about 1/7 to about 1/3 of the fluid velocity through the outlet conduit. The second container (20, 22) is also designed to provide a depth of fluid flow of about 0.02 to about 0.04 inch.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	ES	Spain	MG	Madagascar
AU	Australia	FI	Finland	ML	Mali
BB	Barbados	FR	France	MN	Mongolia
BE	Belgium	GA	Gabon	MR	Mauritania
BF	Burkina Faso	GB	United Kingdom	MW	Malawi
BG	Bulgaria	GN	Guinea	NL	Netherlands
BJ	Benin	GR	Greece	NO	Norway
BR	Brazil	HU	Hungary	PL	Poland
CA	Canada	IT	Italy	RO	Romania
CF	Central African Republic	JP	Japan	SD	Sudan
CG	Congo	KP	Democratic People's Republic of Korea	SE	Sweden
CH	Switzerland	KR	Republic of Korea	SN	Senegal
CI	Côte d'Ivoire	LI	Liechtenstein	SU	Soviet Union
CM	Cameroon	LK	Sri Lanka	TD	Chad
CS	Czechoslovakia	LU	Luxembourg	TG	Togo
DE	Germany	MC	Monaco	US	United States of America
DK	Denmark				

FLEXIBLE BAG ASSEMBLY FOR MAGNETIC SEPARATORBACKGROUND OF THE INVENTION

The present invention is directed toward a flexible
5 container assembly useful for medical applications, and in
particular, a flexible tube set having at least a first
flexible container used in the selective magnetic particle
separation of specific biologics from a heterogeneous
mixture.

10 Magnetic separation of specific biologics from a
heterogeneous mixture involves bringing the heterogeneous
mixture into contact with paramagnetic particles that bear
biologically active compounds which selectively react to
bind the specific biologics to the particles. Typically,
15 the biologically active compounds are antibodies, i.e.
monoclonal or polyclonal antibodies, which selectively bind
to specific biologics, i.e. cells, virus, bacteria,
antigens or other antibodies.

The container in which the heterogeneous mixture and
20 magnetic particle are admixed is placed within a magnetic
field. This magnetic field retains the particles within
the container while the remainder of the heterogeneous
mixture is removed.

A more detailed explanation of magnetic separation as
25 used in medical applications can be found in United States
Patent Nos. 3,970,518, and 4,018,886, both of which issued
to Giaever, 4,219,411, issued to Yen et al, and 4,710,472,
issued to Sauer et al. Many different devices have been
proposed to carry out this magnetic separation. Examples
30 of such devices are disclosed in these various patent
references.

A disadvantage with many such devices is the inadequate
retrieval of the paramagnetic particles from the
heterogeneous mixture caused by the inadequate capture of
35 the particles in the applied magnetic field. Those

particles not held within the magnetic field are free to be carried off with the heterogeneous mixture. This is particularly disadvantageous where the heterogeneous mixture will be returned to the patient.

5 Various devices have been suggested to overcome this deficiency; for example, the device disclosed in the Saur et al patent. This device allows for the movement of the magnets with respect to the container which increases the exposure of the particles to the effects of the magnetic
10 field. Another device which has been developed to overcome this deficiency is disclosed in United States Patent Application Serial Number 397,067, which is continuation-in-part of Serial Number 255,214, and of which this application is a continuation-in-part. This magnetic
15 separator utilizes two different types of magnets for entrapping the paramagnetic particles. The first magnet to which the mixed heterogeneous mixture and paramagnetic particles are exposed possesses a relatively large magnetic field reach. This provides a greater penetration of the
20 container volume. The sacrifice is that the resulting magnetic field strength is lessened. A second magnet is positioned downstream from this first magnet which possesses a smaller magnetic field reach but a higher field strength. The second magnet acts upon all those
25 paramagnetic particles which escape the first magnet. The arrangement of the magnets increases the capture of the paramagnetic particles.

While the magnetic separators disclosed in the discussed patent applications promote efficient capture of
30 substantially all of the paramagnetic particles, it would be beneficial to increase this potential and thus limit the possibility of any of the particles being carried along with the heterogeneous mixture.

to promote the attraction of the magnetic field. While the flexible container arrangement disclosed in the described application is adequate for the purposes of the invention, it would be beneficial if a flexible container arrangement could be provided which assisted the magnetic separator described in the related patent application or other types of magnetic separators in the separation of paramagnetic particles from heterogeneous mixtures.

10 SUMMARY OF THE INVENTION

The present invention is directed at a flexible container arrangement useful for performing the magnetic separation of paramagnetic particles from a heterogeneous biological mixture. In particular, the flexible container arrangement of the invention includes two or more flexible containers having inlet and outlet ports, with at least one outlet port of a first container being connected by a fluid pathway to an inlet port of a second container.

The first container is dimensioned to hold a large volume of a heterogeneous mixture and paramagnetic particles, with the cross-sectional area being from about 20in² to about 50in². The depth of the first flexible container ranges from about 1/4 inch to about 1/2 inch. It should be noted that "depth" for the purposes of this application, is the distance of the cross-section of the container as seen as "C" in Figure 4B, which is the height of the fluid flow path through the container over the magnet. This flexible container is designed to be arranged over a magnet assembly having a relatively large field reach.

The second container is designed to be arranged over a magnet assembly having a relatively small field reach. This is accomplished by providing that the depth of the container is relatively small in comparison to that of the first container. Further, the second container is designed

to limit the flow rate of the fluid from the inlet to the outlet, and also to ensure that the fluid flow is substantially laminar and orderly while minimizing stagnant flow area in the container. This enhances the capture of the paramagnetic particles passing through the container.

The flexible container assembly also preferentially includes one or more flexible containers which are connected to the second container for receiving fluid therefrom by multiple fluid pathways.

BRIEF DESCRIPTION OF THE DRAWINGS

The present invention may be better understood and the advantages will become apparent to those skilled in the art by reference to the accompanying drawings, wherein like reference numerals refer to like elements in the several figures, and wherein:

FIGURE 1 is a prospective illustration of the flexible container assembly of the invention in position on a magnetic separator device;

FIGURE 2 is a top view of an integrally formed container assembly including the first and second containers;

FIGURE 3 is a top view of another embodiment of the invention in which the first and second containers are coupled together by interconnecting tubes;

FIGURES 4A-B are top and side views of the second flexible container of the invention; and

FIGURES 5A-C are top views of different embodiments of the invention showing multiple configurations of receiving containers connected to the second flexible container.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

The present invention is directed to a flexible container assembly useful for medical applications. The flexible container assembly of the invention has particular applicability in the area of magnetic separation. Magnetic

separation is the technique used to isolate specific biological substances from a heterogeneous mixture. Typically this type of technique is used to isolate specific cells, viruses, bacteria or antibodies from a bodily fluid, e.g. blood.

Magnetic separation utilizes paramagnetic particles, such as those manufactured by the Dynal Company of Great Neck, New York. The surface of the paramagnetic particles is chemically treated to attach or bind a biologically active compound. The biologically active compound functions to react with and bind to the specific biologics. Typically, the biologically active compound is an antibody, i.e. a monoclonal or polyclonal antibody for the specific biologic.

The heterogeneous mixture is admixed with the paramagnetic particles in a container. After the expiration of a sufficient amount of time to ensure the reaction between the biologically active compound and the specific biologic, a magnetic field is introduced into the container. This is usually accomplished by placing the container adjacent to a magnet. The paramagnetic particles are thus drawn towards the magnetic field and held along a wall of the container. The remainder of the heterogeneous mixture is then removed from the container leaving the paramagnetic particles and the specific biologic therein.

As described above, investigators have proposed numerous designs for the magnetic separator which increases the exposure of the particles to the magnetic field, thus increasing the probability of capturing the paramagnetic particles. The present invention is directed at a container design which maximizes the magnetic attractive force on the particles.

This is accomplished by designing the container to include at least two separate but aseptically connected flexible containers. The first container is designed to

provide sufficient volume to contain the mixture of the heterogeneous mixture and paramagnetic particles. Usually, the admixing of the heterogeneous mixture and paramagnetic particles will be performed in this first container. The first container is positioned adjacent a first magnet or portion of a first magnet, which magnet possesses a large field reach.

A substantial majority of the particles in the first container are drawn down to the magnet and held against the container wall. The remaining mixture is then drawn out of the first bag and delivered to a second container through an aseptically sealed fluid pathway. As the mixture flows out of the first bag, some paramagnetic particles also leave and flow out of the first bag.

The second container is designed to promote two functions. The first function is to reduce the distance between any fugitive paramagnetic particles which escaped the first magnet and the surface of the second magnet. The second function is to reduce the velocity of the fluid traversing the container. These two functions cooperate to ensure a maximum exposure of the paramagnetic particles to a magnetic field. In this regard, the second container is positioned adjacent a magnet. This magnet may be the same as that against which the first container is positioned, or another type of magnet.

In accordance with a preferred embodiment, the second container is designed to cooperate and enhance the effect of that magnet over which it is positioned. This magnet possesses a magnetic reach relatively less than the first magnet, but has a greater field strength along this reach.

Either way, the limiting of the depth of the fluid pathway flowing through the second container increases the exposure of the paramagnetic particles to the magnetic field. Further, the design of the second container to limit or lower the fluid velocity increases the residual

time that the paramagnetic particles are being exposed to the magnetic field. This further enhances the capture of a substantial portion of the paramagnetic particles.

5 While the flexible container assembly of the invention may be used with various magnetic separator devices, it will be described with specific relation to the magnetic separator described and claimed in United States Patent Application Serial Number 397,067, which is continuation-in-part of Serial Number 255,214, and of which this
10 application is a continuation-in-part. Accordingly, the entire disclosure of the magnetic separator and description of the flexible collapsible containers is incorporated herein by reference.

15 It should be noted that a flexible container assembly is described in general terms in these two applications. The flexible container assembly of this invention is an improvement over this generally taught assembly. Accordingly, those specific descriptions of the flexible container made in these two applications are specifically
20 incorporated herein by way of reference.

Referring to Figure 1, a prospective view of a magnetic separator device, as described in the above incorporated to patent application, is seen generally at 10. Magnetic separator 10 includes a lower base member 12 atop which
25 sits upper base member 14. Formed in the upper base member 14 are two receptacles 16 and 18. The receptacles 16 and 18 are generally rectangularly shaped with four circumference sides and a bottom. The top portion of each receptacle 16 and 18 is defined by hinged plates 24 and 26.
30 A magnet assembly, not seen, is positioned in or on the bottom of each receptacle 16 and 18. A more thorough description of the magnetic assemblies can be found in the above referenced patent application 397,067, with such description specifically incorporated herein by reference.

Each receptacle 16 and 18 is designed to receive a flexible container or bag, seen generally at 20 and 22. The flexible containers 20 and 22 comprise the flexible container assembly of the invention. Generally, the two
5 containers 20 and 22 are connected by a flexible tubing, seen at 28. The flexible tubing 28 lays within a channel 30 interconnecting the receptacles 16 and 18. The flexible containers 20 and 22 include one or more inlet and outlet
10 ports, not shown. An outlet port of flexible container 20 is connected to the inlet port of the flexible container 22 via the flexible tubing 28 to provide a fluid pathway between the two flexible containers 20 and 22.

The flexible container 22 also includes an outlet port from which extends another flexible tubing 32. This
15 flexible tubing 32 fits within a slot 34 formed in the upper base member 14. The flexible tubing 32 is positioned in a roller pump assembly 36, and is used to draw out fluid held in the flexible container 20, through the flexible container 22 and out of the flexible container assembly
20 through the flexible tubing 32.

While not seen in Figure 1, a plurality of receiving containers may be connected to the flexible tubing 32 to receive the fluid exiting the flexible container assembly. The flexible container assembly may be a single integral
25 piece or be formed from one or more detachable sub-assemblies. In one embodiment, as seen in Figure 2, the individual flexible containers 20 and 22 are connected by a single piece of tubing 28. In another embodiment, as seen in Figure 3, the single piece of tubing 28 is divided
30 into two segments 28' and 28'', which are coupled together via a spike and slip assembly, seen generally at 38.

As stated, the outlet of flexible container 22 may be connected to one or more receiving containers. As seen in Figures 5A-C, the outlet of flexible container 22 may be
35 connected to two receiving bags 40 and 40' (Fig. 5A); three

What is claimed is:

1. A flexible container assembly comprising:

a first flexible container having inlet and outlet ports; and

5 a second flexible container having inlet and outlet ports with an inlet port being connected to an outlet port of said first flexible container by a fluid pathway, said second flexible container further having an outlet port connected to a second fluid pathway, said second flexible
10 container being designed to provide for a reduction in fluid velocity therethrough at a rate of from about $1/7$ to about $1/3$ of fluid velocity through said second fluid pathway, said second flexible container further being designed to provide a depth of fluid flow of about 0.02 to
15 about 0.04 inch.

2. The flexible container assembly of claim 1 wherein said second flexible container is designed to provide for a uniform fluid flow from said inlet to said outlet ports.

20

3. The flexible container assembly of claim 2 wherein said second flexible container is designed to provide said depth of said fluid flow of about 0.02 to about 0.04 inch.

25 4. The flexible container of claim 3 wherein said second flexible container is designed to provide reduction of fluid flow therethrough at a rate of from about $1/7$ to about $1/3$.

30 5. The flexible container assembly of claim 4 wherein said second flexible container is formed with walls adjacent said inlet port diverging away from said inlet port to provide an angle to the centerline of said inlet port of from about 35° to about 43° , and is formed with walls
35 adjacent said outlet port converging towards said outlet

port to provide an angle to the centerline of said outlet port of from about 35° to about 43°.

5 6. The flexible container assembly of claim 4 wherein said second flexible container is formed with walls adjacent said inlet port diverging away from said inlet port to provide an angle to the centerline of said inlet port of about 39°, and is formed with walls adjacent said outlet port converging towards said outlet port to provide an angle to the centerline of said outlet port of about 39°.

7. The flexible container assembly of claim 6 wherein said first flexible container has a cross-sectional area of from about 20 to about 50 square inches.

15 8. The flexible container assembly of claim 7 wherein said first flexible container has a cross-sectional height of from about 1/4 to about 1/2 inch.

20 9. A magnetic separator assembly comprising:

a magnetic separator device having two magnetic areas of different field strengths and reaches, a first area having a larger field reach with a lower strength than said second area which has a smaller field reach and a higher strength;

25 a fluid pathway defined by at least two flexible containers, a first of said flexible containers including inlet and outlet ports which is positioned adjacent said first magnetic area, a second of said flexible containers being positioned adjacent said second magnetic area, including inlet and outlet ports with an inlet port being connected to an outlet port of said first flexible container by a fluid pathway, said second flexible container further having an outlet port connected to a second fluid pathway, said second flexible container being
30 designed to provide for a reduction in fluid velocity
35

therethrough at a rate of from about $1/3$ to about $1/7$ of fluid velocity through said second fluid pathway, said second flexible container further being designed to provide a height of fluid flow of about 0.02 to about 0.04 inch.

5

10. The magnetic separator assembly of claim 9 wherein said second flexible container is designed to provide for a uniform fluid flow from said inlet to said outlet ports.

10 11. The magnetic separator assembly of claim 10 wherein said second flexible container is designed to provide said height of said fluid flow of about 0.02 to about 0.04 inch.

12. The magnetic separator assembly of claim 11 wherein
15 said second flexible container is designed to provide reduction of fluid velocity therethrough at a rate of from about $1/3$ to about $1/7$.

13. The magnetic separator assembly of claim 12 wherein
20 said second flexible container is formed with walls adjacent said inlet port diverging away from said inlet port to provide an angle to the centerline of said inlet port of from about 35° to about 43° , and is formed with walls adjacent said outlet port converging towards said
25 outlet port to provide an angle to the centerline of said outlet port of from about 35° to about 43° .

14. The magnetic separator assembly of claim 13 wherein
30 said second flexible container is formed with walls adjacent said inlet port diverging away from said inlet port to provide an angle to the centerline of said inlet port of from about 35° to about 43° , and is formed with walls adjacent said outlet port converging towards said outlet port to provide an angle to the centerline of said
35 outlet port of from about 35° to about 43° .

1/2

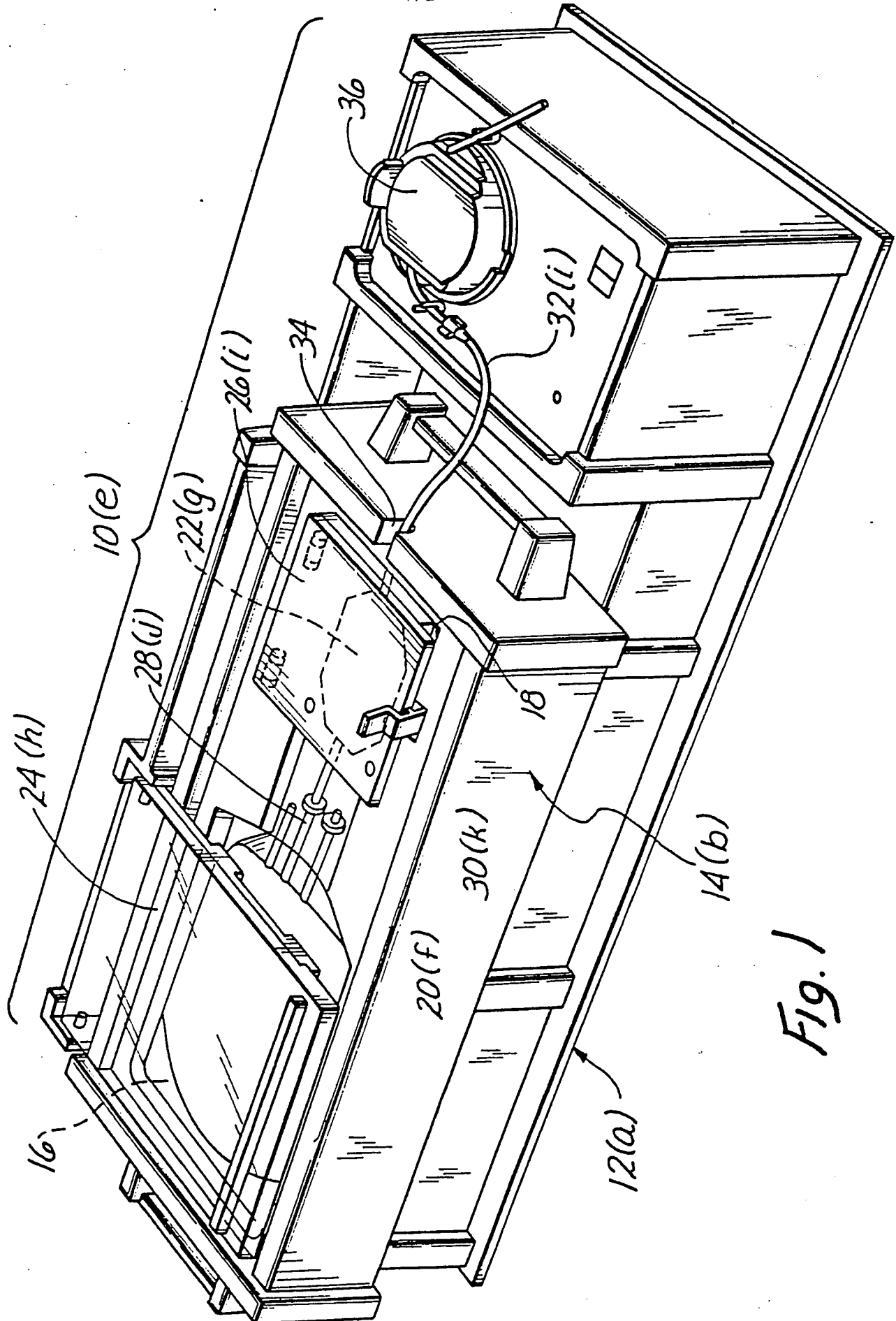


Fig. 1

2/2

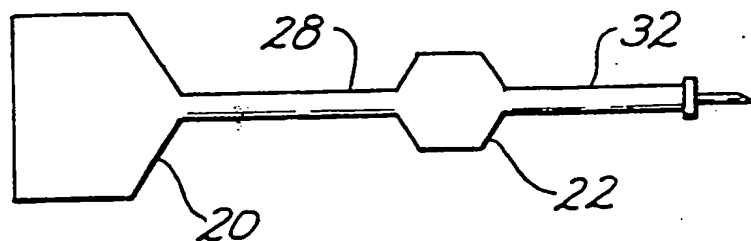


Fig. 2

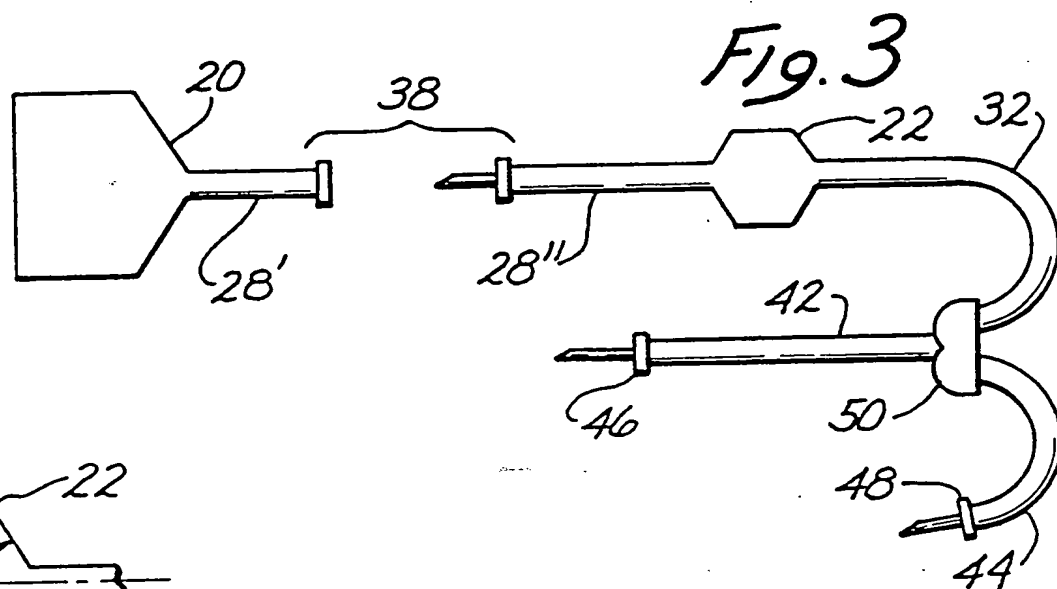


Fig. 3

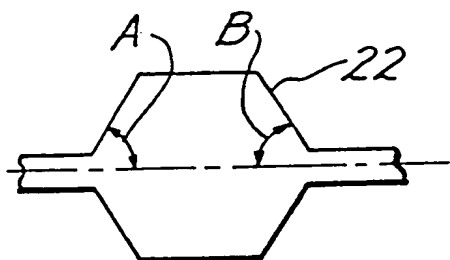


Fig. 4a

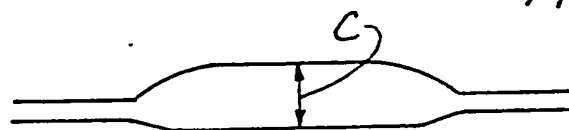


Fig. 4b

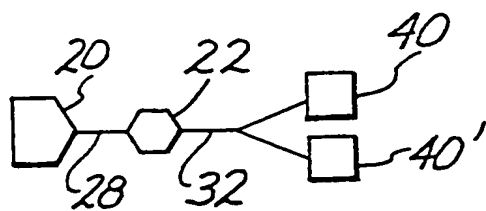


Fig. 5a

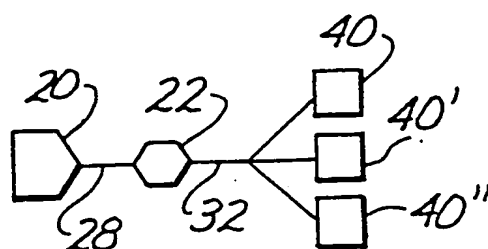


Fig. 5b

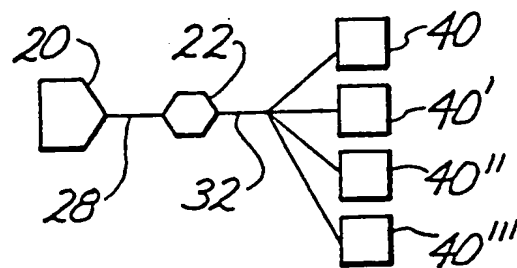


Fig. 5c

